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Efficient Formation of Benzylic Quaternary Centers via Palladium Catalysis

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The benzylic quaternary center is a widely prevalent motif[1] in a multitude of biologically active natural products,[2] drug candidates, and fragrances. The challenge of installing these centers in a straightforward and selective manner continues to receive much attention in recent literature.[3] Transition-metal catalysis offers a spectrum of reactions to address this challenge.[4] In this respect, few reactions have enjoyed the success, tenability, and reliabilty of conjugate addition reactions to β,β-disubstituted enones. For this reaction, whilst catalysis by copper[5] has been successful for the use of reactive organometallics such as Grignard,[6] organozinc,[7] and organoaluminium[7,8] reagents, excellent reactivity with soft organometallics such as boronic acids,[9] borates,[10] and boroxines[11] has been achieved with rhodium.[12]

As a complementary strategy, benzylic quaternary center formation using boronic acids via palladium catalysis would be an important addition to the toolbox of the synthetic chemist, especially in view of scale-up. Following a pioneering disclosure by Lin and Lu,[13] this area has witnessed a flurry of investigations, such as the development of asymmetric versions by Stoltz et al.[14] and ourselves,[15] the application of boroxines for diastereoselective conjugate additions to substituted enones,[16] desulfitative couplings of aryl sulfinic acids,[17] γ-arylation of α,β-unsaturated aldehydes,[18] in addition to a thorough study of the mechanism by computational chemistry.[19]

Arylboronic acids[20] have emerged as the reagents of choice for the introduction of aryl moieties by transition-metal catalysis, especially owing to their commercial availability, easy handling under ambient conditions, and functional-group compatibility. Thus, a practical strategy that affords benzylic quaternary centers employing arylboronic acids, with acceptable palladium loadings would be highly beneficial. This would alleviate the need to dehydrate boronic acids to boroxines or use forcing and strongly acidic conditions to allow loss of SO_2, as in the desulfitative reactions. Furthermore, no studies have documented trends in reactivity of enones or boronic acids depending on their substitution pattern, and essentially all literature examples are limited to cyclic substrates (Scheme 1).

We adopted the reaction of 3-methyl cyclohexenone (**1**) with phenylboronic acid (**2**; Table 1) as a model for studying the various reaction parameters . Our initial efforts focused on the study of *N*,*N*′-bis-2,6-xylyl-acenaphthenequinonediimine (BIAN), a ligand we had previously found to be highly active for oxidative Heck reactions under mild conditions,[21] and has been documented to strongly ligate cationic late-transition metal species. While no reactivity was observed with $Pd(OAc)_2$ (entries 1,2), full conversion was achieved using 5 mol% of $Pd(O_2CCF_3)_2$ (entry 6). Disappointingly, the conversion dropped significantly when the catalyst loading was lowered (entry 7), warranting a search for another catalyst providing high conversions at low catalyst loadings. We were delighted to find that full conversion was obtained with 1 mol% of $Pd(O_2CCF_3)_2$ and 1.5 mol% of 2,2′-bipyridine, when the reaction was performed at 60 °C (entry 10). Performing the reaction at lower temperature, or with an increased proportion of water, resulted in a lower conversion (entry 11, 12). Substituting phenylboronic acid by potassium phenyltrifluoroborate (**4**, entry 13), potassium trihydroxyphenylborate (**6**, entry 14) or phenyl *N*-methyliminodiacetic acid MIDA boronate (**7**, entry 15) did not lead to product formation.

With the optimized conditions [1 mol% $Pd(O_2CCF_3)_2$, 1.5 mol% 2,2-bipyridine, 60 °C, MeOH:H_2O (9:1)] at hand, we went on to explore the scope and limitations of the reaction with a series of cyclic substrates. We were pleased to note that isolated yields exceeding 90% were observed for most of the products resulting from 3-methyl-cyclohexenone and 3-methyl cyclopentenone (Scheme 1). 3-Methyl-cycloheptenone afforded **9** in 80% yield. When comparing the reactions of 3-methyl-cylopentenone and 3-methyl-cyclohexenone with identical arylboronic acids, products resulting from the 5-membered ring substrate usually formed in a higher yield, and the reactions proceeded faster (Scheme 1; **3–3i** and **8a–8g**). This may be due to the larger release of ring strain from a 5-membered cyclic enone as compared to a 6-membered cyclic enone, upon conjugate addition. Nonetheless, substrates **10** and **11** bearing bulky substituents were found to be unreactive under these reaction conditions. This was recently explained by Houk et al.,[19] who calculated that this reaction faces a large barrier for the insertion step, if bulky substituents are present at the β-position. Compared to the catalyst system of Lu et al., our system employs the same Pd loading (1 mol% Pd), but alleviates the low-yielding route to preform the cationic hydroxo-complex.[13] Compared to the system of Lee et al., our protocol employs 5-fold lower loading in Pd.[16]

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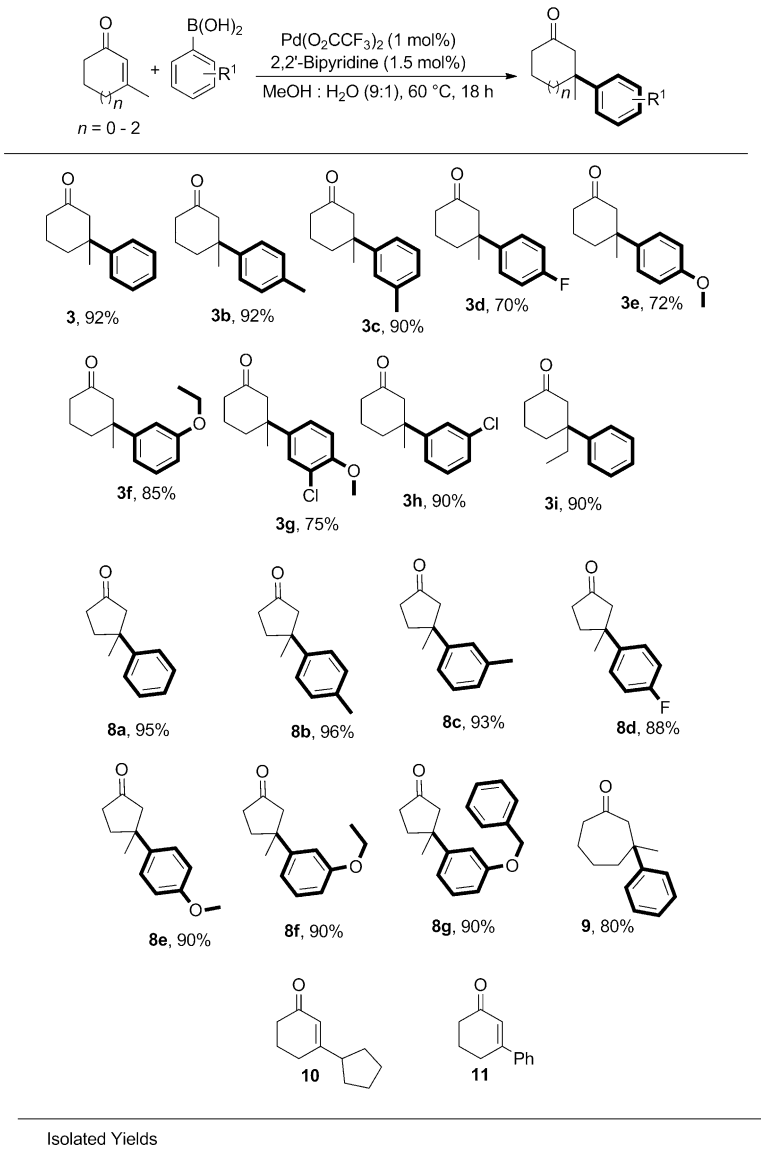


Scheme 1. Conjugate addition of arylboronic acids to cyclic enones.

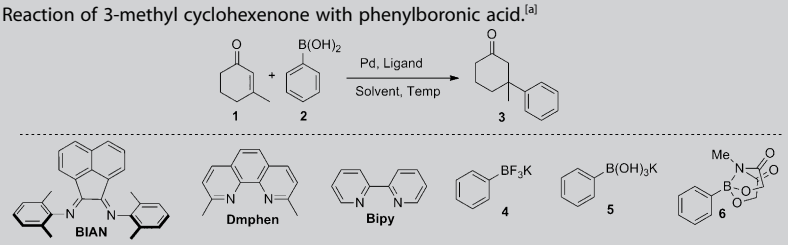
Following the success of the cyclic substrates, we proceeded to investigate whether acyclic substrates could undergo arylation using this catalytic system. In practice, reaction conditions for the conjugate addition to acyclic substrates are usually considerably different from those of cyclic substrates. This could originate from the presence of different conformations in acyclic substrates.[5,22] In addition, release of (ring) strain as in cyclic substrates is absent.

Based on earlier studies from our group,[15] in which we reported that the presence of an allylic oxygen moiety was critical for the success of the reaction, we chose to evaluate the reaction using **12** as test substrate (Table 2). The use of the optimized conditions for cyclic substrates only led to 20% conversion after 36 h (entry 1). Increasing the catalyst loading to 5 mol% led to an improved conversion, though it remained incomplete, even at higher temperature (entries 2 and 3). At this point, we considered the use of additives to improve the conversion. We found that adding 20 mol% of potassium hexafluoroantimonate ($KSbF_6$) to the reaction afforded full conversion (entry 4). The choice of $KSbF_6$ was based on our previous studies on the enantioselective conjugate addition to cyclic enones[15] in which the use of SbF_6^- as a counter-ion for the cationic Pd complex resulted in improved yield and selectivity. Therefore, we surmised that adding $KSbF_6$ to the current reaction system could have a similar influence, and this was indeed found to be the case. The improved activity upon the addition of SbF_6^- may be attributed to a salt metathesis between the trifluoroacetate ($CF_3CO_2^-$) ion and SbF_6^- leading to catalytically more active species.[23] Alternatively, decomposition of the anion would provide fluoride that can activate the arylboronic acid for transmetallation. However, lowering the catalyst loading to 1 mol% in the presence of the additive, gave diminished conversions (entry 5), though still higher than in the case where no additive was present (entry 5 vs. entry 1). Hence it was decided to use 5 mol% of Pd for subsequent experiments.

Scheme 2 represents a study of the scope and limitations of the reaction with acyclic substrates. Phenylboronic acid afforded **13** in 72% yield, while *p*-tolylboronic acid gave **13b** in 75% yield. *p*-Fluorophenylboronic acid gave **13c** in 70% yield. In general, boronic acids bearing alkoxy functionalities performed well in the reaction. Compounds **13d**–**13h** were all obtained in yields between 72–78%. Substrate *E*-**14**, bearing a benzyl moiety was also found to be applicable in conjugate addition under the optimized reaction conditions. Phenylboronic acid and *m*-tolylboronic acid afforded **15a** and **15b** in 74% and 90% yield, respectively. Substrate *Z*-**14** also afforded **15a**, albeit in a slightly reduced yield of 68%. In order to ascertain whether the observed success of substrates **12** and **14** was due to the coordination of the allylic oxygen atom to the metal center during the catalysis, and additionally to test the amenability of a nitrogen-containing substituent in the reaction, substrate **16** was designed. However, this substrate was found to be unreactive. Thus it remains unclear whether the observed influence of the allylic oxygen on the reaction is due to a coordination of the substrate to the metal or due to an electronic influence.

In summary, we report a simple and highly active catalyst system for the formation of benzylic quaternary centers from arylboronic acids and β-disubstituted enones. For cyclic substrates, only 1 mol% of palladium is required for full conversion, and a variety of arylboronic acids could be reacted with yields exceeding 90%. 5-Membered cyclic enones were found to be most reactive, followed by 6-membered rings and then 7-membered rings. This trend may be explained by the release of ring strain upon conjugate addition. Among the arylboronic acids studied, in general, electron-rich boronic acids provided the highest yields. In the case of acyclic substrates 5 mol% Pd was found to be necessary, along with the addition of 20 mol% $KSbF_6$ to afford the highest conversion, along with

Table 1. Reaction of 3-methyl cyclohexenone with phenylboronic acid.[a]



Entry	Pd catalyst	Amount [mol%]	Ligand	Amount [mol%]	Solvent	*T* [°C]	Conv.[b] [%]
1	$Pd(OAc)_2$	5	BIAN	7	$MeOH/H_2O$	RT	0
2	$Pd(OAc)_2$	5	BIAN	7	$MeOH/H_2O$	40	0
3	$Pd(MeCN)_4(BF_4)_2$	5	BIAN	7	MeOH	RT	14
4	$Pd(O_2CCF_3)_2$	5	BIAN	7	MeOH	RT	33
5	$Pd(O_2CCF_3)_2$	5	BIAN	7	$MeOH/H_2O$	RT	43
6	$Pd(O_2CCF_3)_2$	5	BIAN	7	$MeOH/H_2O$	60	full
7	$Pd(O_2CCF_3)_2$	1	BIAN	1.5	$MeOH/H_2O$	60	35
8	$Pd(O_2CCF_3)_2$	5	dmphen	7	$MeOH/H_2O$	60	–
9	$Pd(O_2CCF_3)_2$	5	bipy	7	$MeOH/H_2O$	60	full
10	$Pd(O_2CCF_3)_2$	1	**bipy**	**1.5**	**$MeOH/H_2O$**	**60**	full
11	$Pd(O_2CCF_3)_2$	1	bipy	1.5	$MeOH/H_2O$	RT	32
12	$Pd(O_2CCF_3)_2$	1	bipy	1.5	$MeOH/H_2O$[c]	60	40
13[d]	$Pd(O_2CCF_3)_2$	1	bipy	1.5	$MeOH/H_2O$	60	0
14[e]	$Pd(O_2CCF_3)_2$	1	bipy	1.5	$MeOH/H_2O$	60	0
15[f]	$Pd(O_2CCF_3)_2$	1	bipy	1.5	$MeOH/H_2O$	60	0

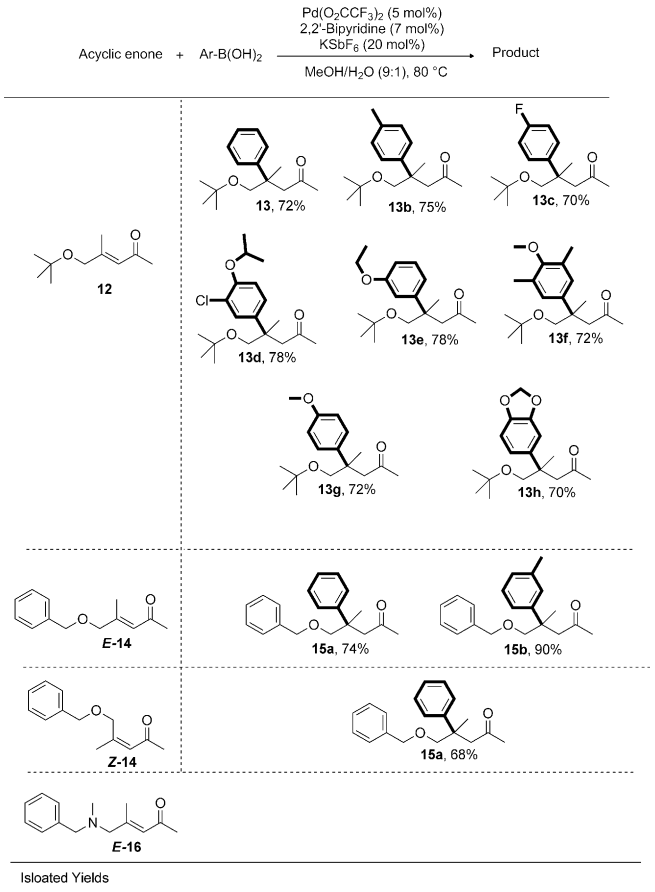
[a] 3-Methyl cyclohexenone (0.5 mmol), phenylboronic acid (1 mmol), Pd precursor, ligand, solvent [$MeOH/H_2O$ (9:1) or MeOH] 1 mL, 12 h. [b] Conversion determined by GC analysis. [c] $MeOH/H_2O$ (4:1). [d] **4** used instead of **2**. [e] **5** used instead of **2**. [f] **6** used instead of **2**.

a higher temperature (80 °C). Both *E* and *Z* alkenes were found to react under the reaction conditions described.

Experimental Section

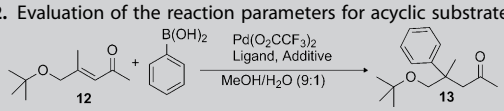
Conjugate addition to cyclic enones: To a Schlenk tube equipped with a magnetic stirring bar and a septum was added palladium trifluoroacetate (3.3 mg, 1 mol%, 0.01 mmol), and 2,2′-bipyridine (2.34 mg, 1.5 mol%, 0.015 mmol). The Schlenk tube was capped and alternated through 3 cycles of vacuum and dinitrogen. The mixture was dissolved in 2 mL of a solution of $MeOH/H_2O$ (9:1) and the tube was placed in a preheated oil bath at 60 °C and allowed to stir for 15 min. The tube was removed from the oil bath, cooled to RT, followed by the addition of the enone (1 mmol, 1.0 equiv) via syringe or pipette and the boronic acid (2 mmol, 2 equiv), in one portion. The septum was replaced by a screw cap. Upon complete consumption of the enone (monitored by TLC/GC), the reaction mixture was allowed to cool to RT and filtered through a pad of silica. The filtrate was dried over $MgSO_4$, concentrated in vacuo, and adsorbed onto silica before being loaded on a silica-gel column. Elution with a mixture of *n*-pentane/ether afforded the corresponding product.

Conjugate addition to acyclic enones: To a Schlenk tube equipped with a magnetic stirring bar and a septum was added palladium trifluoroacetate (8.3 mg, 5 mol%, 0.05 mmol), 2,2′-bipyridine (11 mg, 7 mol%) and $KSbF_6$ (27.5 mg, 20 mol%, 0.2 equiv). The Schlenk tube was capped and alternated through 3 cycles of vacuum and dinitrogen. The mixture was dissolved in 2 mL of a solution of $MeOH/H_2O$ (9:1). The tube was placed in a preheated oil bath at 80 °C and allowed to stir for 15 min. The tube was removed from the oil bath, cooled to RT, followed by the addition of the enone (0.5 mmol, 1.0 equiv) via syringe or pipette and the boronic



Scheme 2. Substrate scope for conjugate addition to acyclic enones.

Table 2. Evaluation of the reaction parameters for acyclic substrates.[a]



Entry	Pd catalyst	Amount [mol%]	Ligand	Amount [mol%]	Additive	*T* [°C]	Conv.[b] [%]
1	$Pd(O_2CCF_3)_2$	1	BIAN	1.5	–	60	20
2	$Pd(O_2CCF_3)_2$	3	dmphen	5	–	80	38
3	$Pd(O_2CCF_3)_2$	5	bipy	7	–	80	63
4	$Pd(O_2CCF_3)_2$	5	bipy	7	$KSbF_6$	80	full
5	$Pd(O_2CCF_3)_2$	1	bipy	1.5	$KSbF_6$	80	45

[a] **12** (0.25 mmol), phenylboronic acid (0.5 mmol), $Pd(O_2CCF_3)_2$, ligand, $MeOH/H_2O$ (9:1) 1 mL, 12 h. Conversion determined by GC analysis.

acid (1 mmol, 2 equiv), in one portion. The septum was replaced by a screw cap. Upon complete consumption of the enone (monitored by TLC/GC), the reaction mixture was allowed to cool to RT and filtered through a pad of silica. The filtrate was dried over $MgSO_4$, concentrated in vacuo and adsorbed onto silica before being loaded on a silica-gel column. Elution with a mixture of *n*-pentane/ether afforded the corresponding product.

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Keywords: arylations · C–C coupling reactions · enones · ligands · palladium

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